A case of haemophagocytic syndrome presenting with oculogyric crises

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J Neurol Neurosurg Psychiatry 2010 81: 469-471
doi: 10.1136/jnnp.2009.177097

evaluation did not detect any symptoms of depression or psychosis. Three years later, the patient has not recovered his personal identity and has retrograde amnesia.

DISCUSSION

Dissociative amnesia is rarer than functional amnesia as reported in the literature. The main symptom is considered to be the loss of personal identity. Hennig-Fast *et al*[3] recently reported the second follow-up study of a patient with persistent retrograde amnesia following a dissociative fugue who exhibited a slight temporal hypometabolism in FDG-PET scan in a resting patient.

Our patient is remarkable in that the relationship between the isolated loss of personal identity for 15 months, retrograde amnesia and functional brain abnormalities involving the medial temporal lobe is documented. Focal retrograde amnesia has rarely been reported in neurological injury. The symptoms and localisations of damage often vary from patient to patient. Functional neuroimaging abnormalities have also been reported in functional amnesia involving the right frontal and temporal cortex. Lastly, few functional neuroimaging studies of conversion hysteria have been reported. Ghaffar *et al*[4] investigated three subjects with unexplained sensory loss using brain fMRI during unilateral and bilateral vibrotactile stimulation. Stimulation of the affected limb did not produce activation of the controlateral primary somatosensory (S1) region, whereas bilateral limb stimulation did. The authors suggested the role of attentional processes in a sensory conversion disorder.

In our patient, hypometabolism involved the left hippocampal and medial temporal regions. Inverse correlations between hippocampus size and memory can be reported in adults and be partly due to the effects of contextual stress. A largely medial, left-sided network of brain regions was found to support verbal memory. The hippocampus is involved in retrograde amnesia, independent of the integrity of memory pathways. These findings suggest that attentional or motivational mechanisms might operate at the level of the hippocampus, at least the left hippocampus, to influence recovery of memory and identity in hysterical conversion even if there is much stronger evidence in support of a relationship between right hemispheric activity and autobiographical retrieval. Efforts to identify the anatomical sites of brain lesions in organic amnesia and a correlation between hypometabolism in specific brain structures have not been contributory, but medial temporal lobe structures seem to be strategic. Regarding this case, we suggest three possibilities, all of which are not necessarily mutually exclusive. First, the patient does in fact have a lesion (of unknown origin) in the left medial temporal lobe. Second, the patient exhibits the consequences of prolonged volitional changes. In our opinion, there are two very speculative possibilities. Finally, the nature of hysterical amnesia could be just such a suppression of memory. This would place the current findings well within the context of knowledge on types of hysterical or psychogenic phenomena. The one feature common to the present case is that the primary cortical area supporting a sensory or motor function is usually hypo-functional in cases of this type.[5] These findings provide a novel framework for a modern psychobiological approach to hysteria, taking into account the symbolic meaning of neurological deficits, the setting in which it emerges, the interaction with the clinician and cultural factors.[5]

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Received 27 September 2009
Revised 24 December 2009
Accepted 11 January 2009

J Neurol Neurosurg Psychiatry 2010;**81**:468–469. doi:10.1136/jnnp.2008.163808

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INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH), also called haemophagocytic syndrome (HPS), is a rare disorder resulting in abnormal proliferation of histiocytes in tissues and organs, including the CNS. HLH can present as a primary disease or occur as a secondary reactive disease. Clinical features are high fever, splenomegaly, cytopenia of two or more cell lines, hypertriglyceridaemia and haemophagocytosis.[1] CNS involvement varies between 10% and 73%, and clinical manifestations include seizures, decreased sensorium, brainstem symptoms, ataxia or demyelinating peripheral neuropathy.[2]

CASE REPORT

A 17-year-old woman, with an unremarkable medical history, was admitted to our hospital with persistent fever for 3 weeks (38–40°C), asthenia, anorexia and myalgias. During the preceding weeks no antibiotic had been started. On examination she was somnolent and when asked to follow a finger she had uncontrolled eccentric eye deviation, left and upwards, lasting for a few seconds and repeated every time this stimulus was presented. There was no behavioural or thought disorder and examination was otherwise normal, without dystonias or meningeal signs. Her body temperature was 38°C and she was haemodynamically stable. The first laboratory investigation disclosed a bicytopenia (normocytic normochromic anaemia, haemoglobin 8.4 g/dl; leucopenia with lymphopenia 2640/330 cell/μl), normal platelets, slightly elevated hepatic and cholestasis enzymes with normal bilirrubin, elevated DHL (1462 U/l) and C reactive protein (89.4 mg/l). Abdominal ultrasound revealed discrete homogenous splenomegaly and hepatomegaly (19 cm). The CT scan showed bithalamic hypodensities, and CSF analysis showed a mononuclear pleocytosis (14 cell/μl), increased proteins (0.63 g/l) and normal glucose (0.55 g/l, CSF/serum 59%). Brain MRI showed T2/FLAIR hyperintensity areas in white and grey matter, with major lesion burden at the level of the thalamus, without increased signal in diffusion weighted images or gadolinium contrast enhancement. There was T1 post-contrast pial/perivascular enhancement in the diencephalic area (figure 1A and B).

During the first 2 days she remained febrile, prostrated and with repeated episodes of oculogyric crises (OGC). By this time there was worsening of blood lineages, and high levels of ferritin (12 790 μg/l) and triglycerides (4.1 mmol/l). In order to exclude a lymphoproliferative disorder, bone marrow aspirate and biopsy were performed revealing haemophagocytosis. On day 3, after an infectious cause had been excluded, including viral encephalitis, and HPS diagnosed, high dose corticotherapy was started (methylprednisolone 1 g intravenous bolus for 3 days, followed by 1 mg/kg/day oral prednisolone). The patient became apyretic and improved her level of consciousness. OGC became progressively rarer and resolved

on day 4 after corticotherapy without any anticholinergic drugs. Follow-up MRI was normal (figure 1C and D). She soon recovered from the cytopenias and all blood chemistry parameters resolved within weeks, as did her spleen and liver dimensions. The following laboratory tests had normal or negative results: IgM serology testing (included Epstein–Barr virus, cytomegalovirus, herpes simplex and varicella zoster virus, leishmania and lyme), HIV, blood and CSF cultures, CSF PCR for herpes virus group and enterovirus, CSF IgG index and lymphocyte immunophenotyping. Immunological study revealed high titres of antinuclear antibodies (1/320) and low IgA, with normal rheumatoid factor, Antineutrophil cytoplasmic antibodies, anti-dsDNA, anti-Sm, anti-U1 RNP, anti-cardiolipin and Sjögren antibodies.

Corticotherapy with oral prednisolone was tapered down and stopped 3 months later. With a follow-up period of 20 months, the patient remains asymptomatic without any treatment, with high titres of antinuclear antibodies (1/320) and low IgA levels. To date, the patient did not fulfil the criteria for any autoimmune disorder.

DISCUSSION

OGC is an acute dystonic reaction of the extraocular muscles, characterised by conjugated eye deviation, usually upward and lateral, lasting from seconds to hours. They were first described in association with epidemic encephalitis lethargica, usually with parkinsonian features and associated thought disorder.[3] OGC have been reported in cases of focal basal ganglia or thalamus lesions. The majority of the reports are associated with neuroleptic medication.[4] To the best of our knowledge, this is the first case of OGC associated with any of the forms of HPS. Clinical and laboratory findings support the diagnosis of HPS, and the abnormalities found in the brain MRI study were strictly in relation to the neurological presentation (decreased level of consciousness and OGC), further supported by the clinical improvement concomitant to the resolution of the diencephalic lesions.[1]

The pathogenesis of OGC remains unclear. However, cytoarchitectural changes involving several structures of the rostral mesencephalon, basal ganglia and/or disturbance of the balance between cholinergic and dopaminergic activity in the basal ganglia and brainstem structures could be responsible for OGC.[3–5] In our patient, in spite of the non-destructive nature of the lesions, the associated oedema probably disrupted the normal cytoarchitecture and local biochemical conditions, disturbing brain circuits and neurotransmission.

HPS should be considered in the differential diagnosis, particularly if neurological dysfunction is associated with prolonged fever, hepatosplenomegaly and cytopenias.[1] In HLH patients with CNS involvement, infiltration of the leptomeninges by lymphocytes and erythrophagocytic histiocytes,

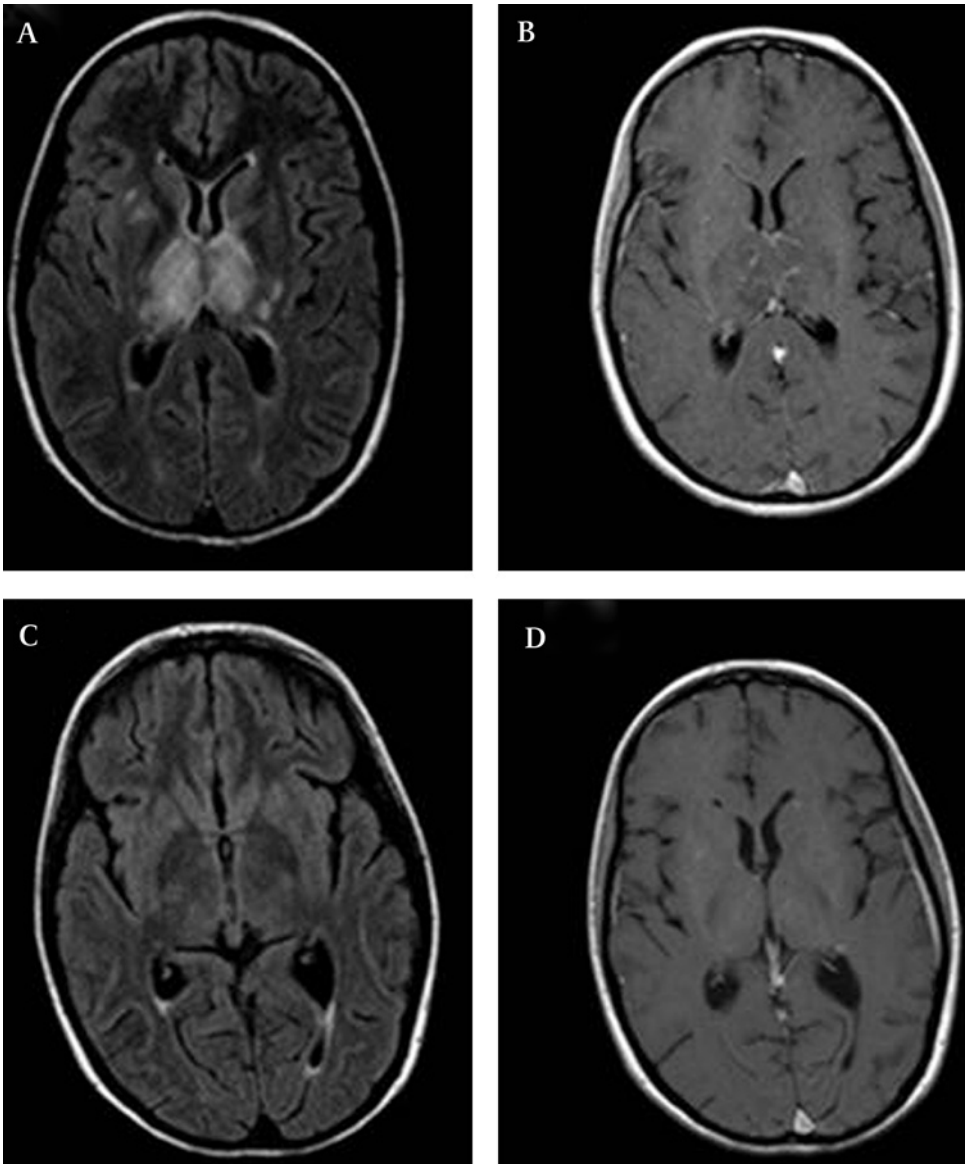

Figure 1 MR imaging. (A) FLAIR image shows hyperintensity areas in white and grey matter, particularly conspicuous in the thalami. (B) Post-contrast T1 weighted image shows pial and perivascular diencephalic enhancement. (C, D) Nine days after treatment. (C) FLAIR image—normal. (D) Post-contrast T1 weighted image shows very discrete leptomeningeal perivascular enhancement in the basal ganglia.

associated with sterile CSF lymphocytosis and elevated protein levels is commonly seen,[2] as observed here. The search for an infectious organism is mandatory and was negative (Epstein–Barr virus, cytomegalovirus, herpes simplex virus, adenovirus, parvovirus B19 and leishmania).[1] Malignant diseases, in particular lymphoma, were considered and excluded. Familial HLH or underlying immune deficiency, specifically Chédiak–Higashi syndrome, Griscelli syndrome or x-linked proliferative syndrome, were highly improbable in our patient because of the absence of family history, age and sex. HPS also occurs in association with autoimmune diseases.[1] Our patient presented with high levels of antinuclear antibodies and low IgA levels that persisted during follow-up. No other laboratory abnormalities or clinical features were present to confirm a specific autoimmune disorder.

In older patients, HPS tends to be less severe, and for patients with HPS associated with autoimmune diseases, corticosteroids with or without ciclosporin are usually sufficient,[1] as observed in our patient. She experienced complete resolution of her symptoms, and after stopping corticosteroids remains asymptomatic (2 years of follow-up).

HPS is a potentially life threatening disorder and neurological manifestations can be the leading symptoms. HPS should be included in the differential diagnosis of OGC. HPS symptoms must be kept in mind, particularly because the decision to treat a febrile and pancytopenic patient with immunosuppressive drugs could be life saving.

Acknowledgements The authors thank Filipe Santos and Inês Freitas, of the Laboratorial Haematology Department of the Hospital Santo António, for their expertise in analysis of the bone marrow aspirate.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Received 7 March 2009
Revised 27 May 2009
Accepted 31 May 2009

J Neurol Neurosurg Psychiatry 2010;**81**:469–471.
doi:10.1136/jnnp.2009.177097

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A MELAS/MERRF phenotype associated with the mitochondrial DNA 5521G>A mutation

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibres (MERRF) are phenotypes that have mainly been associated with mitochondrial tRNA gene point mutations. Clinical and genetic heterogeneity is also recognised and sometimes features of MERRF and MELAS can be found during the clinical course of some patients.[1] These overlapped phenotypes have been related to other mtDNA point mutations (www.mitomap.org).

Here we report a patient with an overlapped MELAS/MERRF phenotype presenting the m.5521G>A mutation, located in the $tRNA^{Trp}$ gene. Biochemical and molecular genetic analysis characterise this transition as a definitively pathological mutation.

PATIENT AND METHODS

A woman developed sensorineural hearing loss at the age of 24 years. At the age of 36 years, she was studied for morning seizures with myoclonic movements in all four limbs. She also suffered from daily headaches and memory loss. Electroencephalography showed irregular point wave complex with a diffuse distribution. A brain CT demonstrated moderate cerebellar atrophy. Evoked auditive potentials had normal latency times and amplitudes below the normal range bilaterally. Psychiatric evaluation showed depressive syndrome. Histomorphological studies in a muscle biopsy revealed the presence of ragged red fibres and a diagnosis of MERRF syndrome was made. In the following years the patient suffered different types of seizures without drug control, persistent headache and weakness in the limbs, as well as cerebellar ataxia and cognitive deterioration. Cochlear implant was performed due to bilateral deafness when she was 41 years old.

At the age of 50 years, she was admitted to hospital for epilepticus status followed by sudden right hemiparesia and aphasia. Brain CT showed a cerebellar vermis hypoplasia and a temporo-parieto-occipital hypodensity with mass effect on the lateral ventricles and the cortical grooves. Blood tests showed lactic acidosis. The patient finally died after deterioration, suffering from malnutrition, hyperthermia and uncontrollable seizures. She was diagnosed with overlapped MERRF/MELAS phenotype. A younger sister had a non-evolutive mental retardation.

All samples were collected with informed consent of the patient and family members, and the study was approved by the Ethics Review Committee of the Government of Aragón (CP24/10/2007). On external examination of the postmortem study, the brain was slightly oedematous, showing slightly collapsed cortical grooves and ventricles (figure 1A, a and b). Areas of laminar necrosis were identified in the brain cortex with no apparent distribution pattern. They were found in all brain lobules but were more abundant in both occipital lobules (figure 1A, c). Histologically, they showed different evolutive phases, with almost complete or total neuronal loss in layers III and V, and a variable intensity gliosis (figure 1B, a). In the cerebellum there was atrophy of the granular layer and a particular de-population of Purkinje cells (figure 1B, b and c). These changes were more intense in the vermis. Gliosis was observed in the posterior horns of the spinal cord. Electron microscopy showed a number of intramitochondrial paracrystalin inclusions in brain blood vessels, endothelium, glial cells, myocytes, myocardiocytes, renal tubular cells and hepatocytes.

Histochemical, biochemical, and molecular genetic studies in muscle were performed using standard procedures.[2 3]

RESULTS

Morphologically, we found ragged red fibres, absence of COX activity and mitochondrial paracrystalin inclusions in the skeletal muscle biopsy of the patient (data not shown). Enzyme activities of muscle mitochondrial respiratory chain revealed a combined deficiency of complexes I, III and IV (74.0%, 77.5% and 37.5% of the lower limit of controls). The mtDNA copy number showed higher (2.2-fold) and normal (1.1-fold) levels in muscle and brain, respectively. Moreover, the search mtDNA deletions and point mutations associated with MELAS or MERRF were negative. Sequencing of the whole mtDNA from brain showed a candidate mutation, m.5521G>A (figure 1C, a) and 12 other reported polymorphysms that defined her as an individual belonging to the H3 haplogroup. The m.5521G>A transition was not found in 5412 patients and controls from all around the world[2 4] and from www.mitomap.org. The possibility of this mutation being a geographically restricted polymorphism was discarded by analysing 47 H3 Spanish individuals. However, this mutation has been previously reported in a patient with a mitochondrial myopathy.[2]